RESEARCH FUNDING ANNOUCEMENT:
RFP LJPC-MA002-18

AN OBSERVATIONAL ASSESSMENT OF THE RENIN ANGIOTENSIN-ADOSTERONE SIGNALLING SYSTEM USING PATHWAY MAPPING

Sponsor:

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FOR QUALIFIED INVESTIGATORS AND THEIR INSITUTIONS ONLY

RFP Release Date: June 19, 2018

Timing: Open

Geographic scope: Global

La Jolla Pharmaceutical Company Objective

The mission of La Jolla Independent Request for Proposal (RFP) mechanism is to partner with the domestic and global healthcare and scientific community to improve patient outcomes and disease state knowledge in areas of mutual interest through support. "Independent" means that the projects funded by La Jolla are the full responsibility of the recipient organization. La Jolla has no influence over any aspect of the projects and only asks for reports about the results and the impact of the projects to share them publicly.

Background

In human physiology, blood pressure is under tight counter regulatory control. The three main systems the body leverages are the sympathetic nervous system, arginine-vasopressin system, and the renin-angiotensin-aldosterone system (RAAS). Angiotensin II (Ang II) is a peptide hormone naturally produced by the body that regulates blood pressure via vasoconstriction and sodium reabsorption [1,2]. The conversion of angiotensin 1 (Ang I) to Ang II is mediated by angiotensin converting enzyme (ACE). ACE is found primarily in the vascular endothelium. After Ang I is converted to Ang II, it has effects on the kidney, adrenal cortex, arterioles, smooth muscle and brain by binding to angiotensin II type 1 (AT) and type 2 (AT) receptors. Ang II binding to the AT1 receptor on vascular smooth muscle cells and tubules, causes vasoconstriction and sodium reabsorption, respectively, leading to elevating blood pressure [2]. In the plasma, Ang II has a half-life of less than ~1 minute, at which point peptidases degrade it into angiotensin III (Ang III) and IV (Ang IV). Ang III has been shown to have 100% of the aldosterone stimulating effect of angiotensin II, but 40% of the pressor effects, while Ang IV has further decreased systemic effect [2]. Conversely, Ang-(1–7) cardiovascular and baroreflex actions counteract those of Ang II [2].

La Jolla completed a Phase 3 study (ATHOS-3), in patients with distributive shock who remain hypotensive despite fluid therapy and vasopressor therapy. The ATHOS-3 trial was conducted using Giapreza, the synthetic form of Ang II drug product produced by La Jolla Pharmaceutical. A total of 344 patients were randomized and 321 patients initiated treatment (Giapreza + standard of care (SOC) or Placebo + SOC). The analysis of the primary efficacy endpoint, defined as the percentage of patients achieving the pre-specified target mean arterial pressure (MAP) response (MAP >/= 75 mmHg or an increase in MAP of >/= 10 mmHg from baseline without an increase in standard of care vasopressor therapy), was statistically significant: 23% of the 158 placebo-treated patients had a MAP response compared to 70% of the 163 Giapreza-treated

patients ($p < 0.0001$). In addition, a trend toward longer survival was observed: 22% reduction in mortality risk through day 28 for Giapreza versus placebo [hazard ratio = 0.78 (0.57 - 1.07), p =0.12] [3]. There was a higher incidence of arterial and venous thrombotic and thromboembolic events in patients who received GIAPREZA compared to placebo treated patients in the ATHOS-3 study [13% (21/163 patients) vs. 5% (8/158 patients)]. The major imbalance was in deep venous thromboses. The Giapreza label recommends use of concurrent venous thromboembolism prophylaxis [3].

Previous reports suggest low Ang II levels and decreased ACE activity predict worse outcomes in sepsis [4]. As part of a pre-specified analysis to assess if Ang I/ Ang II ratio predicts outcomes in distributive shock, Ang I and Ang II were measured at baseline prior to study treatment in ATHOS-3. Ang I and Ang II, and Ang I/Ang II ratio were dichotomized by median value [5]. A relative low Ang II state, as assessed by higher Ang I/ Ang II ratios (>1.63, median across the study population), was associated with higher mortality across the study population (HR=1.78; 95% CI: 1.25 – 2.53, p=0.002). The risk of death within the placebo arm was significantly associated with an elevated Ang I/ Ang II ratio, in the Ang II treated arm, the high ratio was attenuated (HR=1.64, 95% CI:0.97-2.79, p=0.066). This attenuation was associated with a significant treatment effect of Ang II compared to placebo on mortality for patients with high Ang I/ Ang II ratio (HR= 0.64; 95% CI: 0.41-1.00, p = 0.047). These data indicate a relative low Ang II state, as assessed by higher Ang I/ Ang II ratio, predicted increased mortality in patients with vasodilatory shock. However, limited data are available on RAAS signaling in septic and distributive shock or other conditions in which mean arterial pressure may be lowered.

The RAAS consists of multiple enzymes, giving rise to a network of effector peptides binding to specific receptors. The RAAS can be classified into two distinct pathways, 1) the classical RAAS, whose main effector peptide is Ang II (Ang 1-8) and 2) the alternative RAAS pathway in which the main effector Angiotensin 1-7 (Ang 1-7), which is known to bind the receptor MAS. The MAS-R system works to counter the effects on MAP mediated by Ang II [2]. The balance between the two branches depends on many co-variates and may be altered in many diseases.

Objective of the RFP:

La Jolla will consider providing research support and supplies for assessment of the RAAS pathway in septic and distributive shock or other conditions in which mean arterial pressure may be lowered.

The content and/or the format of the RFP initiative and its related materials must be designed in such a way that it addresses the objectives listed below.

RAAS Mapping by Attoquant Diagnostics GmbH

RAAS-Fingerprint analysis can be used to quantify either circulating or equilibrium angiotensin levels. While equilibrium analysis is an optimal tool to assess the soluble RAAS in clinical serum samples, circulating peptides require special sampling precautions, involving protease inhibitor stabilization during sample collection.

The dynamic nature of the RAAS with very short angiotensin metabolite half-lives (seconds) as well as rapid on-going angiotensin formation via renin are sources of contradicting angiotensin data in the literature. It is essential to thoroughly control the whole process from sampling down to signal detection, assuring the integrity and reproducibility of angiotensin data. This requires sampling in the presence of a special optimized angiotensin protease inhibitor cocktail or adhering to sophisticated sample analysis protocol.

RAAS mapping will be performed using LC-MS/MS based assays by Attoquant Diagnostics GmbH (Österreich, Austria). La Jolla will provide RAAS sampling tubes with inhibitor cocktail (added to every tube) to Principle Investigator (P.I.).

La Jolla sponsored RAAS Components measured in Attoquant System*:

- Ang I, Ang II, Ang II, Ang IV, Ang 1-7, Ang 1-5
- Ang 1-9, Ang 2-10, Ang 2-7, Ang 3-7
- Bradykinin 1-8, Bradykinin 1-7, Bradykinin 1-5
- Aldosterone

**Preference will be given to proposals that encompass all RAAS components*

Given the considerations listed above and to help ensure data continuity across studies, the following will be conducted during the RFP approval process and contract set-up:

- Respond and submit research proposal (with experimental plan – see below)
- La Jolla shipment of Attoquant Diagnostics tubes to Principal Investigator (P.I.) site
- Collection of research sample and appropriate storage of samples
- Shipment of sample tubes from P.I. Site to Attoquant Diagnostics GmbH in Österreich, Austria (Paid by La Jolla)
- Data analysis and sharing to P.I. from Attoquant Diagnostics
- Publication

Proposal Submission Requirements

In the submission email header indicate that this is in response to RFP code: RFP LJPC-MA002-18. When responding to this RFP, please follow the established guidelines for the La Jolla research grant submission process Proposal Format (see below) .

All applications and supporting documents must be submitted to MAresearch@ljpc.com

Research Proposal applications submitted after August 31, 2018 will not be reviewed.

Proposal Format Guidance:

Section 1. General Information

- Include Investigator Agreement
- Investigator information (name, email, phone, institution, address, CV)
- Country(s) where study will be conducted
- Products
- Study title
- Study duration (number of months, estimated start and end dates)
- Resources requested (study drug and/or funding)
- Proposed Budget

Section 2. Study Design

- Study hypothesis (medical/scientific question to be addressed)
- Background & rationale
- Study objectives
- Inclusion/exclusion criteria (if applicable)
- Study design/schedule (including treatments/procedures)
- Patient population
- Study endpoints
- Publication and statistical plan
- Reference

Proposals should be submitted electronically through the LJPC MA Research portal at MAresearch@ljpc.com

Evaluation Criteria

- Submitted proposals will be evaluated according to the following criteria:
  - Completeness of the proposal, addressing each of the requested sections in this RFP
  - Experience and successful track record of implementing quality improvement initiatives
  - Familiarity with the disease area – understanding its pathology, treatment, current issues Proposed initiative structure and delivery options
  - Number and type of patients included in the initiative, tube allocation and feasibility
  - Type and setting of disease state
  - Length of initiative (feasibility to complete in proposed time)

- Qualifications and credentials of researchers, analysts, statisticians, and other quantitative skills represented in the staffing plan to conduct analysis
- Documentation of program results (i.e. outcomes reported, publication plan of the results, etc.)
- Clarity of proposal and budget
- Fiscal responsibility
- Collaboration with a national society or association, a medical or academic institution, or other non-profit organizations and governmental agencies
- Timely submission

Funding Guidelines

La Jolla will provide Direct funding associated to the shipment and analysis of the RAAS mapping tubes only.

Decision Date and Notification

You will receive an acknowledgement email upon receipt of your application. Once the Committee has reached a decision, a Response Letter will be sent via email, followed by a letter of acceptance if the request was approved.

Please contact Antonio E. Civitarese at acivitarese@ljpc.com if you have any questions regarding this RFP.

References:

1. Ince, C. The microcirculation is the motor of sepsis. Crit Care. 2005; 9: Suppl 4: p. S13-19.
2. Patel S, Rauf A, Khan H, Abu-Izneid T. Renin-angiotensin-aldosterone (RAAS): The ubiquitous system for homeostasis and pathologies. Biomedicine & Pharmacotherapy. 2017; 9: 317-325.
3. Zhang W, Chen X, Huang L, Lu N, Zhou L, Wu G, Chen Y. Severe sepsis: Low expression of the renin-angiotensin system is associated with poor prognosis. Exp Ther Med. 2014; 7: 1342-1348.
4. Khanna A, English SW, Wang XS, et al.; for the ATHOS-3 Investigators. Angiotensin II for the treatment of vasodilatory shock. N Engl J Med. 2017; 377(5):419-430.
5. Wunderink RG, Albertson TE, Busse LW, Deane AM, Khanna A, McCurdy MT, Ostermann M, Young PJ, Chavez AN, Handisides DR, Chen S, Chawla LS, Tidmarsh GF, and Bellomo R. Baseline angiotensin levels and ACE effects in patients with vasodilatory shock treated with angiotensin II [abstract]. In: Intensive Care Medicine Experimental 2017 5(Suppl 2):0703.